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**Bipolar affective disorder and borderline personality disorder:
Differentiation based on the history of early life stress and
psychoneuroendocrine measures.**

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Abstract

Introduction: Borderline Personality Disorder (BPD) and Bipolar Affective Disorder (BD) have clinical characteristics in common which often make their differential diagnosis difficult. The history of early life stress (ELS) may be a differentiating factor between BPD and BD, as well as its association with clinical manifestations and specific neuroendocrine responses in each of these diagnoses. **Objective:** Assessing and comparing patients with BD and BPD for factors related to symptomatology, etiopathogenesis and neuroendocrine markers.

Methodology: The study sample consisted of 51 women, divided into 3 groups: patients with a clinical diagnosis of BPD (n = 20) and BD (n = 16) and healthy controls (HC, n = 15). Standardized instruments were used for the clinical evaluation, while the history of ELS was quantified with the Childhood Trauma Questionnaire (CTQ), and classified according to the subtypes: emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. The functioning of the hypothalamic-pituitary-adrenal (HPA) axis was evaluated by measuring a single plasma cortisol sample.

Results: Patients with BPD presented with more severe psychiatric symptoms of: anxiety, impulsivity, depression, hopelessness and suicidal ideation than those with BD. The history of ELS was identified as significantly more prevalent and more severe in patients (BPD and BP) than in HC. Emotional abuse, emotional neglect and physical neglect also showed differences and were higher in BPD than BD patients. BPD patients had greater severity of ELS overall and in the subtypes of emotional abuse, emotional neglect and physical neglect than BD patients. The presence of ELS in patients with BPD and BP showed significant difference with lower cortisol levels when compared to HC. The endocrine evaluation showed no significant differences between the diagnoses of BPD and BD. Cortisol measured in patients with BPD was significantly lower compared to HC in the presence of emotional neglect and physical neglect. A significant negative correlation between the severity of hopelessness vs cortisol; and physical neglect vs cortisol were found in BPD with ELS. The single cortisol sample showed a significant and opposite correlations in the sexual abuse diagnosis-related groups, being a negative correlation in BD and positive in BPD.

Discussion: Considering the need for a multi-factorial analysis, the differential diagnosis between BPD and BD can be facilitated by the study of psychiatric symptoms, which is more severe in the BPD patients with a history of early life stress. The function of the HPA axis assessed by this cortisol measure suggests differences between BPD and BP with ELS history.

Conclusion: The integrated analysis of psychopathology, ELS and neuroendocrine function may provide useful indicators to differentiate BPD and BD diagnoses. These preliminary data need to be replicated in a more significant sample with a better assessment and multiple assessments of the HPA axis activity.

Key words: Borderline Personality Disorder; Bipolar Affective Disorder; Early Life Stress; Hypothalamic-pituitary-adrenal (HPA) Axis; Cortisol; Abuse and Neglect

Introduction:

The concept of Borderline Personality Disorder (BPD), as defined in the DSM-III in 1980, emerged from Gunderson and Singer's review [1] that identified alleged descriptors in the areas of dysphoric affect, impulsive action, interpersonal relationships, quasi-psychotic cognitions and poor social adjustment. By 1994, when DSM-IV was completed, more than 300 studies on BPD had been conducted and most of the revisions in the diagnostic criteria represented refinements that were intended to increase the distinction between BPD and similar disorders, such as Bipolar Affective Disorder (BD) and Narcissistic Personality Disorder [2]

Nevertheless, the differentiation between BPD and BD remains a challenge in the clinical setting, with the difficulty in establishing the differential diagnosis between these disorders mainly due to the clinical characteristics they have in common, especially emotional instability and impulsivity [3, 4]. In addition, comorbidity is common: approximately 20% of bipolar II patients are diagnosed with comorbid BPD, compared to 10% of bipolar I patients [5,6]. Also, in this context, the concept of the bipolar spectrum has been proposed to expand the BD diagnosis to include a wider range of syndromes, notably BPD [7-9].

To help determine the differential diagnosis between BPD and BD, the relationship between these disorders has been analyzed under several aspects: evaluation of co-occurrence, familial prevalence, response to medication, phenomenology, longitudinal course and aetiology [10-13]. The results of these studies provide sometimes controversial and inconclusive data, but recent evidence indicates that biological factors and psychosocial factors may be more significant in BPD than in BD [14].

Association between early stress and BD and BPD diagnoses

Although we consider the aetiology of mental disorders generally as multi-factorial, genetic factors and the occurrence of traumatic events in the life history of patients are identified as the primary factors associated with vulnerability to developing a psychiatric disorder [15-21]. Evidence from the literature demonstrates a positive association between early life stress (ELS) and the development of both BPD and BD [22-25]. In addition, many subsequent clinical and neurobiological changes have been linked to the occurrence of ELS. Suicidal behavior and hallucinations are linked with ELS in both BPD [26,27] and BD [28-30]. Additionally, in BPD, a history of ELS is associated with changes in the function of the HPA axis [31], the volume of the hippocampus and amygdala, as well as the cerebral blood flow in the recall of traumatic memories [32]. In BD, the literature has highlighted associations with changes in BDNF levels [33] and a worse clinical course, measured by hospitalisations, rapid cycling, depressive episodes, and quality of life [34-37].

However, assessments of different types of early stress and their respective associations with BD and BPD diagnoses are controversial and show conflicting results. While some results indicate an association of sexual abuse history with the development of BPD symptoms [18,38,39], other studies report that sexual abuse is not significantly associated with an increased risk for BPD [40-42]. Additionally, other studies have highlighted the role of emotional abuse, as a particular type of early stress, finding a more consistent association with both diagnoses [26, 41,43]. Specifically considering BPD [38], reported borderline symptoms were significantly correlated with physical abuse but not with neglect.

Functioning of the hypothalamic-pituitary-adrenal axis and response to stress

The endocrine response to stress is characterised by the activation of the HPA axis and associated with effects of cortisol; these are beneficial when related to an acute action, but may have deleterious pathological consequences during chronic activation [44, 45].

Given these actions in response to stress, the link between trauma in childhood and psychopathology in adulthood may be related to the HPA axis, which remains unstable, hyper-stimulated, vulnerable or dysfunctional after being hyperactive during the development process, possibly due to the transcriptional/ epigenomic mechanisms that alter its functioning [46]. Thus, the occurrence of traumatic events in childhood impacts the efficacy with which an individual can respond to stress in the long term, as a result of the modifications observed within neuroendocrine circuits.

Previous literature has identified that the risk of psychopathology in adults is related to a complex interaction of multiple factors associated with the HPA axis - reflecting the range of individual vulnerability observed in response to various types of stress impacting on the development of mental disorders. The identification of a stress biomarker, such as cortisol, could provide useful information about the diagnoses of BPD and BD, and aid in the distinction of etiopathogenic aspects related to the history of early life stress, manifested by neuroendocrine changes. Thus, we evaluated and compared patients with the diagnoses of BPD and BD, seeking to identify differential indicators between these disorders related to the symptoms of anxiety, impulsivity, depression, hopelessness, suicidal ideation and mania; the history of early life stress; and the functioning of the HPA axis.

Methodology

The methodology used a cross-sectional design, from a single psychometric and neuroendocrine evaluation of 51 participants who either had a clinical diagnosis of BPD (n=20) or BD (n=16), or were healthy control volunteers (n=15). Prior to enrolment, participants underwent screening interviews by two Senior Psychiatrists (AKM and MFJ) using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) for the major DSM-IV diagnoses and the SCID-II for Personality Disorder diagnoses, to confirm diagnoses in accordance to the DSM criteria. The severity of psychiatric symptoms, such as anxiety, depression, hopelessness and suicidal ideation, and impulsivity, was assessed through Beck's: Anxiety Inventory (BAI), Depression Inventory-II (BDI-II), Hopelessness Scale (BHS) and Suicidal Ideation Scale (BSI) respectively. Additionally, the Young Mania Scale was used as a measure for manic symptomology. The history of early life stress was investigated by the Childhood Trauma Questionnaire (CTQ), and classified according to the subtypes: emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect.

The inclusion criteria specified patients aged between 18 and 60 years, presenting with a clinical diagnosis of BD or BPD, according to DSM-IV-TR criteria and currently receiving psychiatric treatment in the psychiatry services of the General Hospital of School of Medicine of the University of Sao Paulo in Ribeirao Preto. All eligible patients were clinically screened for comorbidities and general medical conditions, according to the SCID-I and II. Both patients with BD and BPD were evaluated whilst in a euthymic state, according to Young Mania Scale (YMS) and DSM-IV current episode.

The control group was composed of healthy volunteers (HC) with a minimum age of 18 years, and without a diagnosed psychiatric disorder and no history of early life stress (ELS). Many of the recruited HC participants included hospital staff, students and members of the local community, and prior to enrolment had to complete a detailed clinical history, in addition to a diagnostic evaluation, to exclude any psychiatric disorders or use of psychotropic medications.

Exclusion criteria for patients were defined by: the presence of comorbidities with either BPD or BP, use of steroids, pregnancy or lactation, serious health conditions or general medical conditions judged likely to underlie cognitive, emotional and behavioural changes. Additionally, patients were excluded if they were using psychoactive substances not prescribed for psychiatric treatment in the last month. For ethical and practical reasons, it was not possible to evaluate patients in a medication-free state.

For the control group, individuals with a diagnosis of a mental disorder or other general medical condition that could present with psychiatric symptoms were excluded from the study.

To measure endocrine activation, fasted blood samples were collected by venipuncture in the early hours of the morning (8am), in order to measure plasma basal cortisol. Participants were instructed avoid engaging in physical activities, stressful situations, consuming large meals prior to the examination and, to the best of their ability, respect the usual sleeping routine. The collected blood samples were stored under appropriate laboratory conditions before being Plasma cortisol was analyzed using a radioimmunoassay technique (RIA) standardized in the Laboratory of Endocrinology of HC-FMRP-USP. The sensitivity of the assays and intra- and inter-assay coefficients of variation were: 1.2 µg/dL, 2.8% and 10.4% respectively. Plasma cortisol measurements are expressed as mcg/ml within the results.

The analysis of data was performed using the SPSS software (Statistical Package for the Social Sciences, version 15.0). A p value of <0.05 was used to define significance throughout.

The socio-demographic, clinical, psychometric and hormonal data were analysed using descriptive statistics. Statistical analyses were performed using the Student's t -test for continuous data and chi-square (χ^2) for categorical data. T-test and analysis of variance (ANOVA) followed by the Tukey's posthoc test was used for multiple comparisons in the groups.

Results

The socio-demographic profile of the study sample was delineated from the identification of variables related to age, marital status, children, schooling and employment status. Whereas, the clinical characterisation refers to severe medical conditions, duration and forms of treatment (drug therapy and psychotherapy). This data is presented in Table 1, distributed by the diagnostic groups, BD, BPD, and HC.

INSERT TABLE 1

Assessment of psychiatric symptomatology

Borderline patients presented with more severe symptoms of depression (BDI), suicidal ideation (BSI), hopelessness (BHS), anxiety (BAI) and impulsivity (BIS) in comparison to the bipolar patients; however, manic symptoms (YMS) were higher in patients with BD. Both patients with BD and BPD were evaluated in euthymia according to YMS and DSM-IV current episode. See details in Table 2

INSERT TABLE 2

Assessment of the early stress history

The assessment criteria defining the presence of a significant history of ELS was a moderate to severe score according to the Childhood Trauma Questionnaire (CTQ). In this way, the participants of each group were subdivided between those without ELS and with ELS. As can be seen in the figure 1, the presence of ELS predominated the diagnostic groups, BD and BPD; however, it was not identified in the control group (HC).

INSERT Figure 1

The comparison of the diagnostic groups, in relation to the presence of ELS, revealed a greater occurrence in the BPD group (80%) compared to the BD (56%), but without statistical significance ($n = 36$; $\chi^2 = 2.36$, $df = 1$, $p = 0.124$).

The quantitative assessment of the ELS history with the CTQ shows results that differentiate BPD, BD and the HC group, as shown in Table 3.

INSERT TABLE 3

The mean total and individual subtype CTQ scores across all three participant conditions are presented in Figure 2.

These results suggest that within our sample, participants with BPD had experienced a greater severity of ELS, with notably higher scores in emotional abuse, emotional neglect and physical neglect.

Additionally, we were able to observe, significant correlations in anxiety, depression, and suicidal ideation with general early life stress, sexual abuse and physical neglect.

INSERT Figure 2

The severity of symptoms evaluated by the BAI, BDI and BSI scales in the BD group were positively correlated with the severity of early stress in relation to sexual abuse and physical neglect. We found a strong correlation between the measures of anxiety and physical neglect ($r = 0.979$; $p < 0.001$), depressive symptoms and early general stress ($r = 0.770$; $p = 0.015$); depressive symptoms and history of sexual abuse ($r = 0.911$; $p = 0.001$); depressive symptoms and physical neglect ($r = 0.750$; $p = 0.020$); suicidal ideation and history of early general stress ($r = 0.715$; $p = 0.030$); suicidal ideation and history of sexual abuse ($r = 0.939$; $p < 0.001$) and suicidal ideation and physical neglect ($r = 0.777$; $p = 0.014$).

Other significant correlations between symptoms and the history of early life stress were evaluated in the BD group. The severity of sexual abuse was positively correlated with symptoms of depression ($r = 0.851$; $p < 0.001$); sexual abuse and suicidal ideation ($r = 0.647$; $p = 0.007$). Likewise, physical neglect had positive correlations with depressive symptoms ($r = 0.698$; $p = 0.003$); and physical neglect with anxiety symptoms ($r = 0.954$; $p < 0.001$), in the BD group.

Endocrine evaluation

Morning plasma cortisol levels differed significantly between groups, with cortisol levels lower in both the BD and BPD groups in comparison to controls (Figure 3). However, there was no difference between the two patient groups. The BD group showed the numerically lowest plasma cortisol levels and also showed lower variance

(s.d.= 3.2), with a small mean difference (1.14 mcg / ml) in relation to the BPD group. Conversely, the control group had the highest and most varied levels (s.d.= 9.9) of plasma cortisol.

Figure 3 presents the results of cortisol compared to the average values amongst the groups.

INSERT Figure 3

Correlations between psychometric measures and cortisol

Correlations between psychometric measures and cortisol were calculated in the whole BPD group for the severity of symptoms. We observed a strong negative correlation between hopelessness, evaluated by BHS, and plasma cortisol ($r = -0.716$ and $p < 0.001$), and a moderate negative correlation between suicidal ideation, assessed by BSI, and cortisol ($r = -0.456$ and $p = 0.043$).

We found a strong negative correlation between the severity of Hopelessness assessed by the BHS and dosage of plasma cortisol in Borderline Personality Disorder patients with history of ELS ($n=16$. $r=-0,709$; $p=0,002$), see figure 4.

INSERT Figure 4

In the BD patients with a history of ELS, no significant correlation was seen between the psychometric measures (depression, hopelessness, anxiety, impulsivity and suicide ideation) and cortisol.

In order to explore if hormonal differences were observed in participants who had experienced different subtypes of ELS, were further analysed these results highlighting

that in just one plasma sample, significant differences were observed between cortisol levels when comparing the controls with the diagnostic groups (BD and BPD). Additionally, the presence of ELS in patients with BPD and BP showed significantly lower cortisol levels compared to controls.

Moreover, we found a negative correlation between the severity of Physical Neglected reported by the CTQ and dosage of plasma cortisol in borderline patients with history of ELS ($n=16$. $r=-0,538$; $p=0,032$), see figure 5.

INSERT Figure 5

Cortisol measured in patients with BPD was significantly lower when compared to the control group in the emotional neglect ($p=0.04$) and physical neglect ($p=0.01$) subtypes.

The cortisol measured in patients with BD was significantly lower when compared to control group in patients without experience of sexual abuse vs. controls ($p=0.04$) and in BD without emotional ($p=0.04$) and without physical ($p=0.04$) neglect vs controls; and in patients with BPD without sexual abuse ($p=0.02$) vs controls. Regarding physical and emotional abuses, we did not find significant differences ($p>0.05$) between patients in the diagnostic groups (BD or BPD) and healthy controls.

From the results obtained with the psychometric evaluations and cortisol levels significant correlations were observed among BD and BPD and history of sexual abuse.

In bipolar patients, the severity of the sexual abuse showed a moderate negative correlation with the plasma cortisol ($r = -0.509$; $p = 0.044$). Sexual abuse and cortisol were positively correlated in patients with BPD ($r = 0.467$; $p = 0.038$), and are represented in the Figures 6 and 7, respectively.

INSERT Figure 6

We did not find significant correlations in either BD or BPD patients between plasma cortisol level and other subtypes of early stress, including emotional abuse, physical abuse, emotional neglect and physical neglect ($p>0.05$).

INSERT Figure 7

Discussion

Clinical diagnoses that rely solely on symptoms render themselves at risk for misdiagnoses. A prime example is the common misdiagnosis between borderline personality disorder and bipolar disorder, due to the sharing of multiple similar clinical features. However, as identified in the aforementioned results, the analysis of psychopathology, ELS and neuroendocrine function, provides some clear differentiating features that may be used to improve clinical diagnoses.

Through the measurement of basal cortisol, our findings suggest that there are identifiable variations in the HPA axis functioning in patients with either BPD or BD and histories of ELS; thus, supporting the previous literature associating ELS with dysregulation of hormonal response(s).

The assessment of psychiatric symptoms in these patients indicates a higher severity of depressive, suicidal ideation, hopelessness, anxiety and impulsivity symptoms in Borderline Personality Disorder, thus suggesting that they are experiencing more severe distress compared to bipolar patients. Another possibility for the more significant severity reported by the patients with BPD regardless of the stage or course of the disease (which involves symptoms such as anxiety and depression [25,47,48], impulsivity [4,6,49], and suicidality [10]) is related to differences in treatment phase or approach.

The prevalence of ELS was considered present if there was a moderate to severe score obtained from the CTQ. For both diagnosis-related groups, the majority of patients had a history of ELS according to this criterion. However, this was observed in a higher proportion in the BPD group in comparison to the BD and HC groups, as also seen in previous literature suggesting a stronger association (60-80%) in patients with BPD than BD (50%) [10, 50-55].

Besides presenting higher prevalence, the group with BPD showed greater severity of early life stress in general . Furthermore, emotional abuse, emotional neglect and physical neglect predominated in BPD, differentiating it from BD. There is currently no similar literature comparing the history of different types of ELS between bipolar and borderline personality disorder. Although it is suggested that there may be differences between the subtype of trauma in childhood or vulnerability to such experience among these diagnoses, the divergent evidence is clear in literature reviews [10, 56].

A comparative study between patients with BPD and Major Depressive Disorder (MDD) observed no difference between the levels of reported physical abuse between patients and a healthy control group and no difference in the severity of ELS was observed between the two diagnoses assessed (BPD and MDD) [57]. Another study evaluating patients with BPD and MDD found differences in regards to the emotional abuse and emotional neglect subtypes, but not in the sexual abuse and physical neglect scores [58].

Within our BPD and BD sample, physical and sexual abuse were present only up to a moderate severity, with no difference between the diagnosis-related groups, and no difference compared to the control group for sexual abuse. Thus, although these forms of maltreatment during childhood are regarded as the most often recognized and disclosed, they proved unrepresentative of the reality of early stress as a whole to which

patients were exposed. Instead, other aspects of early life stress seem to be more significant: emotional abuse, emotional neglect and physical neglect [59]. Although it is reported that the sexual abuse is a factor associated with the development of several mental disorders, especially BPD and BD [38, 39, 60, 61], this association is controversial and not supported by other studies [40-42, 62]. Similarly, there are disagreements about the role of physical abuse in the development of these disorders [43, 63,64]. Therefore, it is important to emphasize the necessity of considering fully all types of ELS in mental health evaluations and developing a perhaps less stereotypical view of childhood trauma, such as viewing violence in just a sexual and/or physical form.

Although less studied, these other forms of abuse and emotional neglect are suggested to significantly influence the development of the neuroendocrine systems and the incidence of psychopathology. This is supported by rodent studies, where we are able to observe sensitisation of the HPA axis in response to psychological stress, but not in response to physical stress [65]. Moreover, comparative studies suggest that, compared to other types of childhood trauma, emotional abuse and neglect are the most significant predictors of psychopathology in adulthood [35]. Emotional abuse is most frequently associated with personality disorders [56], whereas emotional neglect has been associated with persistent effects on the psychological and neurobiological constitution, such as low self-esteem, problems in interpersonal relationships, depressive and anxiety symptoms, all of which may imply a higher risk of developing a personality disorder [56, 66-70] and in BD is also associated with a more unfavorable course [71].

By measuring plasma basal cortisol, we were able to obtain a measure of the functioning of the HPA axis, with our results suggesting a more impaired functioning in both BPD and BD in comparison to HC as seen in the lower cortisol concentrations recorded. Regarding the cortisol profile in BPD, hypoactivity of the HPA axis, similar to the results

observed in our study, is reported in the literature [72,73]. On the other hand, elevated basal cortisol levels have also been observed, which has previously been linked to a suppressed inhibitory feedback of the HPA axis [74], and comorbid depression [75].

Regarding BD, these results contrast with some parts of the literature that indicate hyperactivity of the HPA axis in bipolar patients, irrespective of their current mood state [76-83]; history of suicidal behaviour [84]; and/or the age of onset of the first episode [85]. These data suggested that these neuroendocrine changes may indicate a genetic vulnerability factor (endophenotype) to BD [86-88].

However, in a study to evaluate naïve patients experiencing their first manic episode, reduced plasma cortisol levels were observed when compared to controls, which is consistent with the findings of our sample. In this study, measurements of plasma cortisol were correlated in diverse ways to mood state, with levels lower in the presence of euphoria and increased in the presence of irritability [89]. Furthermore, normal cortisol levels were reported in another study [90]. Additionally, similar finding was identified in patients with BD without a history of suicidal behavior or earlier age of onset [84,85].

Correlational analysis between the types of ELS and cortisol presents enlightening results. Thus, it was observed that plasma cortisol levels and sexual abuse were correlated in both diagnostic-related groups, but in opposite ways. Thus, in BPD, the level of cortisol was positively correlated with sexual abuse, while the correlation was negative in BD, i.e., higher levels of cortisol are associated with lower scores of sexual abuse in this group. Thus, the results of our study indicate that in BPD patients, the history of sexual abuse could stimulate the functioning of the HPA axis consistent with reports in the literature [31]; while in patients with BD, a more inhibitory response is observed. However, it is essential to consider that sexual abuse in borderline personality and bipolar patients was identified as mild or at minimal levels of severity, as discussed

earlier. This might indicate that even when the reported severity of sexual abuse is not severe, based on normative CTQ scores, it may still affect the neuroendocrine profile of these subjects significantly.

Some studies on the association between history of ELS, and the functioning of the HPA axis, highlight the relevance of identifying the subtype of the stressor. However, these studies show varying and inconsistent results, besides being not specific to, and comparative between, the diagnoses of BPD and BD. There is evidence to indicate an association of sexual abuse with hyperactivation of the HPA axis [91], and emotional abuse with decreased cortisol reactivity [92], besides reports of an association between emotional neglect and physical abuse and low cortisol levels [91-93]. In relation to these data in the literature, our findings are in agreement with the role of sexual abuse in the hyperactivation of the HPA axis in borderline personality patients. Lee et al. conducted a study on BPD patients with a history of ELS, using the same instruments used in our study, and identified a pattern of reduced functioning of the HPA axis (decreased levels of cortisol) correlated with the emotional neglect subtype [94,95].

However, our data are preliminary and have some limitations and should be interpreted with caution. We have assessed a small sample of 51 subjects, with just 16 BD (31%), 20 BPD (39%) and 15 healthy controls (30%). This small sample size limits the confidence with which we can conclude there is an opposite direction correlation of cortisol and CTQ sexual abuse between the BPD and BP groups. Another aspect that should be carefully considered is that only one sampling of plasma cortisol was taken. A single cortisol measure has been described in some studies in the past as correlating of HPA axis activity [96,97]; however, most studies have at least taken two or three samplings, or assessed on two or more days, in an attempt to get a more reliable

measurement of endogenous cortisol levels and HPA axis function [98, 99, for review see 100].

As mentioned before, the baseline functioning of the HPA axis could be influenced in several ways, and respond in different ways according to each subtype of ELS. In addition, our results identified that HPA axis functioning, as measured by plasma cortisol, also varies when comparing patients with BP and BPD. For instance, patients with BD showed lower plasma cortisol as the severity of sexual abuse increased, whereas the opposite pattern held in BPD patients. Additionally, a negative association was identified between emotional neglect and physical neglect and plasma cortisol levels in BPD patients. These differences suggest that with an understanding of a patients' specific ELS history, we could use biomarkers, such as cortisol, to further support and improve the accuracy of either a BPD or BP diagnosis, due to these unique and differential biological presentations. However, these findings are still preliminary and, thus, would need further evaluation and replication, in a larger sample, to further assess differences in HPA axis activity in BPD and BP before they could be implemented in clinical settings.

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of interest to declare. Only the authors were involved in the study design and preparation of this report.

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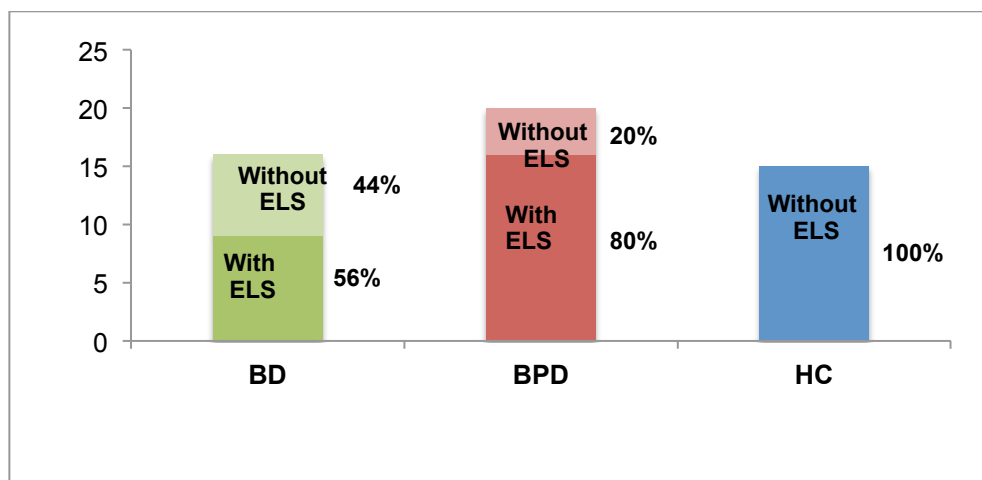


Figure 1- Distribution of the subjects of the diagnostic BD and BPD(n = 36) and control (n = 15) groups classified as having early life stress (with ELS) or without early life stress (without ELS).

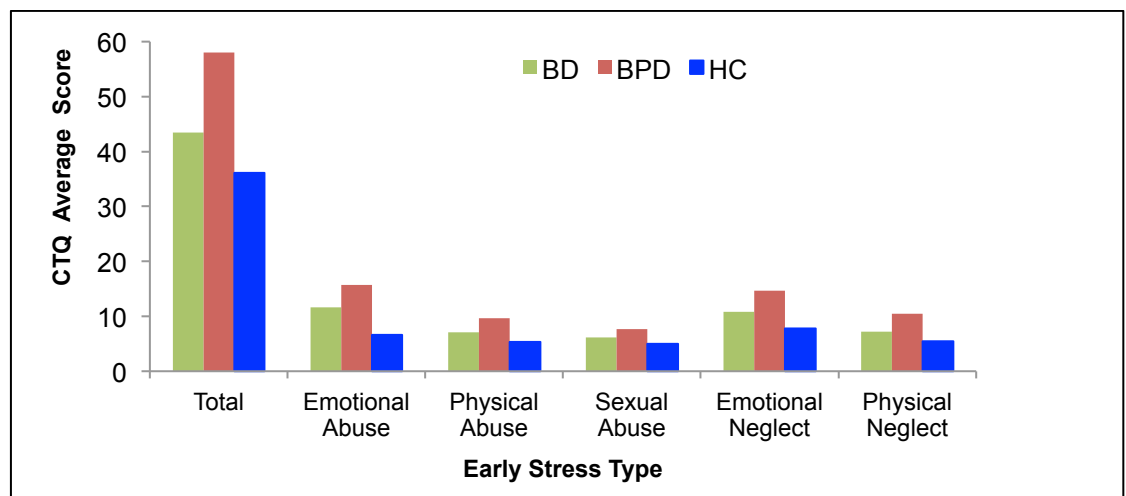


Figure 2. Distribution of scores of early stress and its subtypes compared between the diagnosis-related groups.

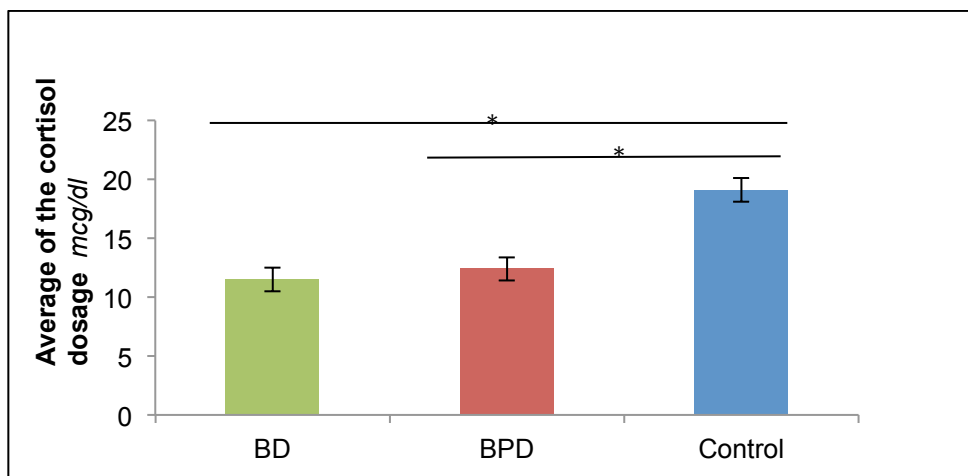


Figure 3 Distribution of the average dosage of basal cortisol among the groups

ANOVA Test. $F = 5.8$; $df\ 2$; $p = 0.005$

BD vs. BPD $p=0,869$

***BD vs. Healthy Controls** $p=0,008$

***BPD vs. Healthy Controls** $p=0,019$

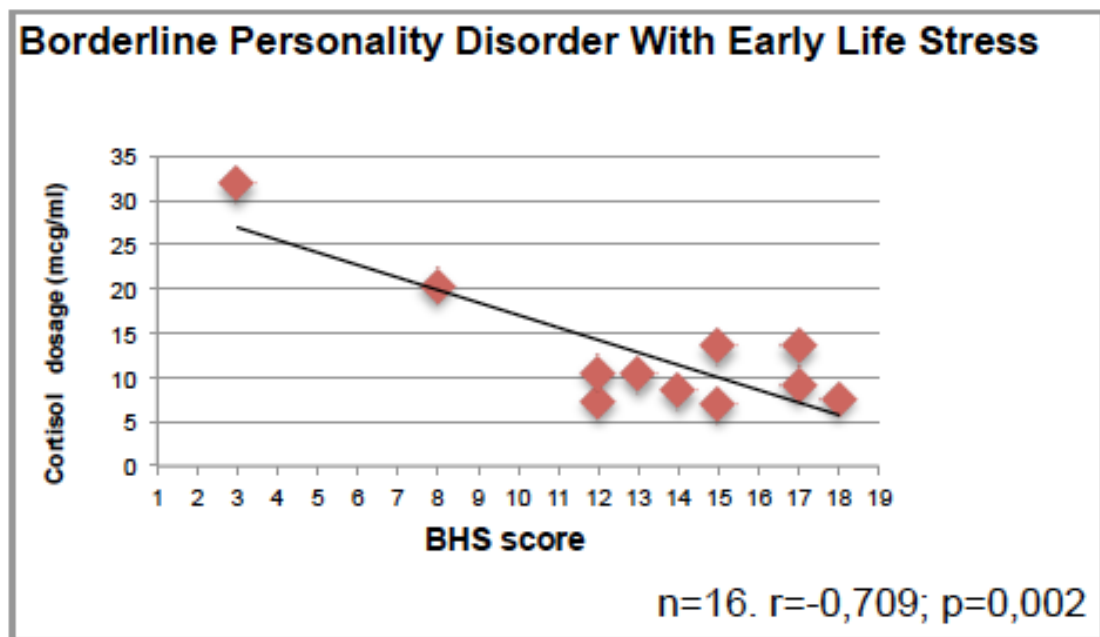


Figure 4. A negative correlation between the severity of Hopelessness assessed by the BHS and dosage of plasma cortisol in Borderline Personality Disorder patients with history of Early life Stress (n=16. $r=-0,709$; $p=0,002$)

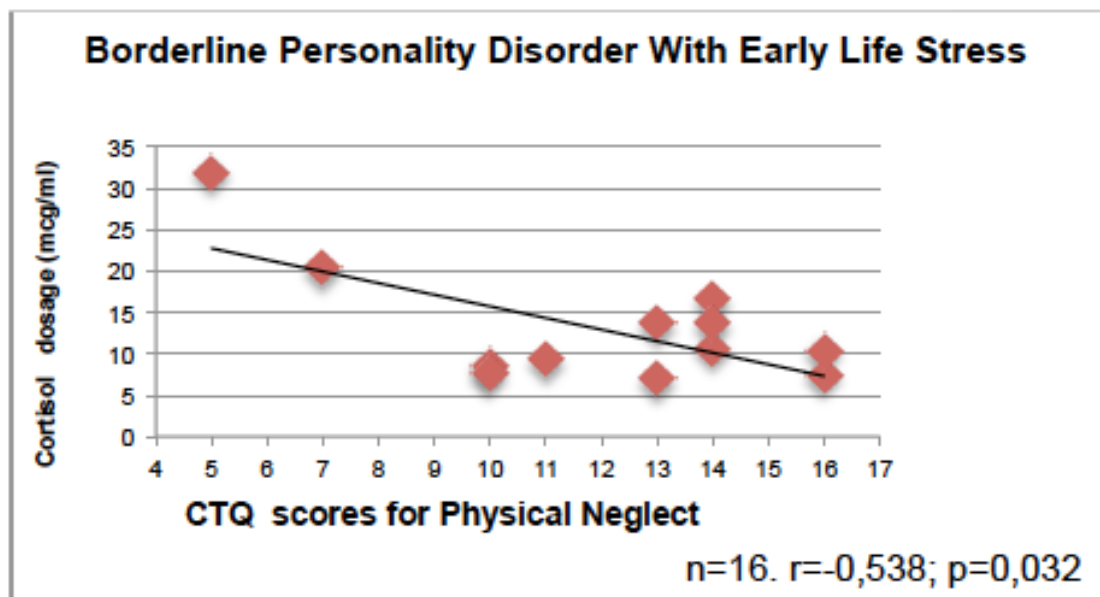


Figure 5. A negative correlation between the severity of Physical Neglected reported by the CTQ and dosage of plasma cortisol in borderline patients with history of Early life Stress ($n=16$. $r=-0,538$; $p=0,032$)

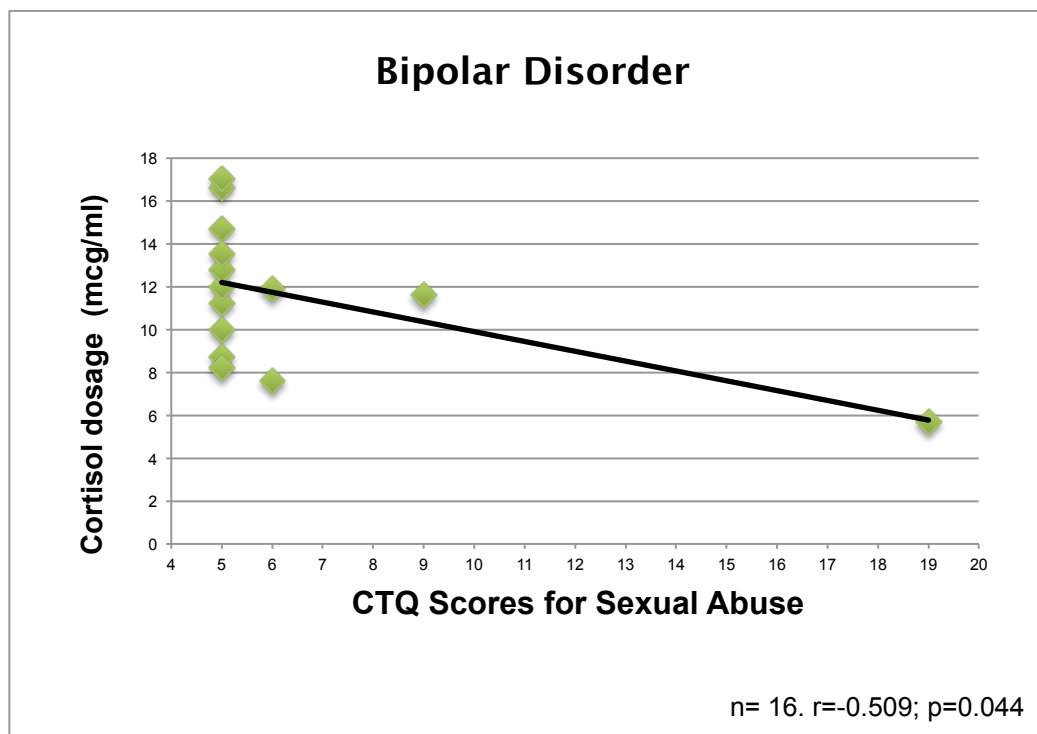


Figure 6. Negative correlation between the severity of sexual abuse reported by the CTQ and dosage of plasma cortisol in bipolar patients (n= 16. $r=-0.509$; $p=0.044$)

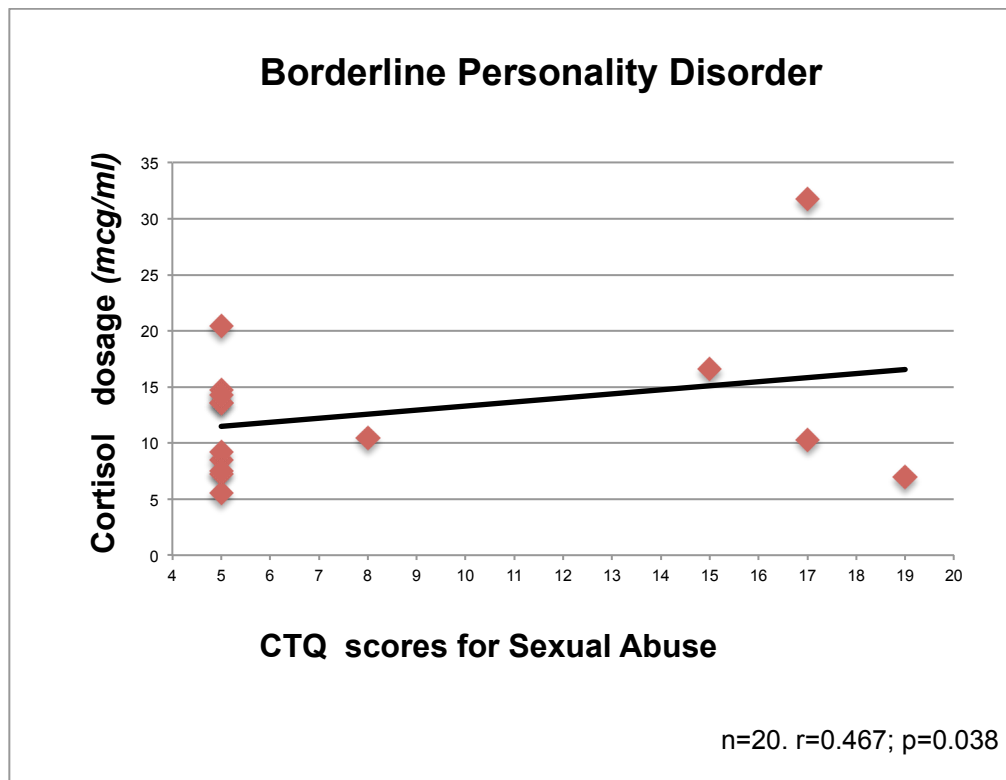


Figure 7. Positive correlation between the severity of sexual abuse reported by the CTQ and dosage of plasma cortisol in Borderline Personality Disorder patients (n= 20 $r=0.467$; $p=0.038$)